In the Drawings:

Please replace existing Figures 1, 2, 4, 6, 8, 10, 12, 13, 15, 16, and 17 with the replacement Figures 1, 2, 4, 6, 8, 10, 12, 13, 15, 16, and 17 enclosed herewith.

REMARKS

In view of the following remarks, the Examiner is respectfully requested to withdraw the rejections and allow Claims 1-12 and 18-30 the only claims pending and currently under examination in this application.

Formal Matters

Claims 1-12 and 18-30 are pending after entry of the amendments set forth herein.

Claims 1-12 and 18-24 were examined. Claims 1-12 and 18-24 were rejected. No claims were allowed.

Claims 1, 3, 5-10, 18-24 have been amended. Support for the amendments can be found in the claims as originally filed and throughout the specification at, for example: page 6, lines 23-37.

New Claims 25-30 have been added. Support for the new claims can be found in the claims as originally filed and throughout the specification at, for example, Figures 6, 8 and 16, and page 32, line 25 though page 35, line 21, lines 16-17.

The specification has been amended in the Abstract and pages 1 and 2 to incorporate the descriptions in Figures 1, 2, 4, 6, 8, 10, 12, 13, 15, 16, and 17.

The specification has also been amended on page 32 to correct a typographical error. Support for the amendment can be found in Figures 1, 8, and 16 at sequence position 63 where glutamic acid (E) was replaced in the wild type (Figure 1) with alanine (A) (Figures 8 and 16).

Figures 1, 2, 4, 6, 8, 10, 12, 13, 15, 16, and 17 have been amended to remove the objectionable description language. Replacement Figures 1, 2, 4, 6, 8, 10, 12, 13, 15, 16, and 17 are provided herewith.

As the above amendments introduce no new matter to the application, their entry is respectfully requested.

Withdrawal of Objections and Rejections

The Applicants express gratitude in the Examiner's indication that objections and rejections not repeated from the previous Office Action, have been withdrawn.

Objection to the Specification

The Office Action has objected to the Abstract for being unclear. As suggested in the Office Action, the Abstract has been amended to remove the objectionable language. Therefore, this objection may be withdrawn.

The specification has also been amended to correct a typographical error. In particular, the specification has amended on pages 32 to correct the point mutation term from "A65E" to "E63A". Support for the amendment can be found in Figures 1, 8, and 16 at sequence position 63 where glutamic acid (E) was replaced in the wild type (Figure 1) with alanine (A) (Figures 8 and 16).

Objection to the Drawings

The Office Action has objected to Figures 1, 2, 4, 6, 8, 10, 12, 13, 15, 16, and 17 for including description language. Figures 1, 2, 4, 6, 8, 10, 12, 13, 15, 16, and 17 have been amended to remove the objectionable description language and replacement Figures 1, 2, 4, 6, 8, 10, 12, 13, 15, 16, and 17 are provided herewith. Therefore, this objection may be withdrawn.

Figures 6, 8, and 16 have also been amended to correct the recited sequences by including the start codon ATG for the nucleic acid sequences and the amino acid methionine (M) for the amino acid sequences.

A corrected Sequence Listing is also provided herewith incorporating the corrections.

Certification Regarding Sequence Listing

I hereby certify that the enclosed Sequence Listing is being submitted under 37 CFR §§ 1.821(c) and (e) in paper and computer readable form (Compact Disk labeled 'CRF').

As required by 37 CFR 1.821(f), I hereby state that the content of the paper and

computer readable copy of the Sequence Listing, submitted in accordance with 37 C.F.R. §1.821(c) and (e) are the same. The Computer Readable Format (CRF), being submitted under 37 CFR §§ 1.52(e) and 1.824, is formatted on IBM-PC, the operating system compatibility is MS-Windows and the file listing is:

Seqlist.txt 41 KB created March 28, 2006.

I hereby certify that the enclosed submission includes no new matter. The Sequence Listing was prepared with the software FASTSEQ, and conforms to the Patent Office guidelines. Applicant respectfully submits that the subject application is in adherence to 37 CFR §§ 1.821-1.825.

Rejection under 35 U.S.C. § 112, first paragraph (New Matter)

The Office Action has rejected Claims 1-2 and 20-24 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. In particular, the Office Action asserts that the limitation "wherein said nucleic acid has a sequence similarity of at least about 75% with a nucleotide sequence of SEQ ID NO:11" is considered to be new matter. The Applicants respectfully disagree.

The specification on page 8, lines 10-15 specifically discloses the language of the amendment:

> In many embodiments, **the nucleic acids have a sequence that is substantially similar (i.e. the same as) or identical to the specific nucleic acid sequences of the figures and sequence listing included herewith** as part of this specification. By substantially similar is meant that **sequence identity will generally be** at least about 60%, usually at least **about 75%** and often at least about 80, 85, 90, or even 95%.

(emphasis added)

The applicants note that the above language provides the adequate support for the amendment. Therefore, the amendment is not new mater. As such, the Applicants respectfully request that this rejection be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph (Enablement)

Claims 1-2, 5-12 and 18-24 have been rejected under 35 U.S.C. § 112, first paragraph, for allegedly not providing enablement for any nucleic acid encoding a far red shifted fluorescent protein or mutant thereof having a sequence similarity of at least about 75%, 80%, or 90% with a nucleotide sequence of SEQ ID NO:11. In view of the remarks made herein, this rejection is respectfully traversed as applied and as it may be applied to the pending claims.

As noted in the Office Action, a specification complies with the statute even if a reasonable amount of experimentation is required, as long as the experimentation is not "undue". One way to determine if undue experimentation is required is to utilize the *Wands* factors.1 However, all of the factors need not be reviewed when determining whether a disclosure is enabling.[2]

The Applicants respectfully submit that when evaluated in view of the relevant *Wands* factors, the specification clearly enables one of skill in the art to practice the subject invention without undue experimentation. In other words, Claims 1-2, 5-12, and 18-24 contain subject matter which is adequately described in the specification in such a way to teach someone how to make and use the claimed invention without having to practice undue experimentation.

---

1 (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims

2 See *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991).

The Applicants note that the courts have clearly taught that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (see also MPEP §2164.01).[3]

The claims of present application are directed to nucleic acids present in other than their natural environment that encode far red shifted chromo- or fluorescent protein, wherein the nucleic acid has a sequence identity of at least 75%, 80% or 90% with SEQ ID NO:11. As provided below, the Applicants maintain that the specification provides ample disclosure to enable one skilled in the art to practice the claimed invention.

For example, the subject nucleic acids are described, for example, on page 6, line 23 through page 16, line 2; the particular far red shifted aspect is described, for example, on page 16, line 7 though page 17, line 2; exemplary methods of producing such mutants are described, for example, on page 18, line 7, through page 19, line 17, and in greater detail on page 31, line 16 through page 32, line 2; resulting exemplary mutants are described at, for example, on pages 32-36; constructs, vectors, expression cassettes, and expression systems including the subject nucleic acids are described, for example, on page 11, line 3, through page 13, line 27; and applications using the subject far red shifted proteins are described, for example, on page 24, line 6, though page 30, line 6.

Moreover, exemplary methods of producing such variants are described, for example, on page 15, line 16, through page 16, line 2, and in greater detail on page 31, line 16 through page 36, line 15. In addition, the specification also provides abundant description for methods of evaluating a far red shifted property on page 16 as well as in the examples section at, for example, pages 32 and 34. Therefore, in view of such guidance provided in the specification, in combination with the knowledge of one of skill in the art, and experimentation that may be necessary is reasonable.

---

3. See also *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom.*, *Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428

In addition, the present application contains working examples demonstrating exemplary mutagenesis protocols for generating the subject nucleic acids encoding the far red shifted proteins (Example A, page 31), examples of mutants generated (Example B, page 32), and exemplary methods of evaluating far red shifted proteins suitable for use with the subject invention (Example III, page 34). As such, the present application does provide a person skilled in the art, through the specification as well as the working example, sufficient enablement for the subject invention.

Furthermore, the Applicants note that the presence or absence of working examples is but one factor to be taken into consideration in determining whether the specification is enabling for the full scope of the claims. Under MPEP § 2164.02 the consideration is whether one skilled in the art would be expected to be able to extrapolate the provided examples across the entire scope of the claim. As presented herein, Applicants argue that it would be reasonable to conclude that one skilled in the art would be able to extrapolate the working examples provided in the specification across the across the entire scope of the claims without excessive and undue experimentation. As such, based on the disclosure provided in the application one skilled in the art would be able to extrapolate the working examples to the full scope of the pending claims.

In sum, the amount of experimentation required to subject invention would not be undue and excessive because working examples have been provided, guidance is given on how to generate such nucleic acids, and one of skill in the art would be able to perform the experiments as a matter of routine. The specification therefore provides sufficient enablement such that one of ordinary skill in the art would be able to practice the invention without undue experimentation. Accordingly, the specification clearly enables the subject invention as demonstrated in view of the relevant *Wands* factors.

(Fed. Cir. 1985).

As such, for at least the reasons described above, Claims 1-2, 5-12, and 18-24 are adequately enabled by the specification. Accordingly, the Applicants respectfully request that the rejection of Claims 1-2, 5-12, and 18-24 under 35 U.S.C. §112, first paragraph be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 1 and 5-6 (Office Action, page 19)

Claims 1 and 5-6 have been rejected under 35 U.S.C. § 112, second paragraph for allegedly indefinite for reciting the phrase "having a sequence similarity". As suggested in the Office Action, Claims 1 and 5-6 have been amended to recite "sequence identity". Therefore, the Applicants respectfully request that this rejection be withdrawn.

Claims 7-10 and 18-24 (Office Action, page 19)

Claims 7-10 and 18-24 have been rejected under 35 U.S.C. § 112, second paragraph for allegedly indefinite for reciting the phrase "having a sequence of similarity". As suggested in the Office Action, Claims 7-10 and 18-24 have been amended to recite "sequence identity". Therefore, the Applicants respectfully request that this rejection be withdrawn.

Claims 8 ad 21 (Office Action, page 20)

Claims 1 and 5-6 have been rejected under 35 U.S.C. § 112, second paragraph for allegedly indefinite for reciting the phrase "mimetic thereof". Claims 8 and 21 have been amended to remove the objectionable language. Therefore, the Applicants respectfully request that this rejection be withdrawn.

Rejection under 35 U.S.C. § 102

Lukyanov et al. (Office Action, page 20)

The Office Action has rejected Claims 3-4, 7-12 and 18-24 under 35 U.S.C. § 102(a) for allegedly being anticipated by Lukyanov et al., JBC 275(34):25879-25882 (2000). In view of the amendments to the claims, this rejection may be withdrawn.

The cited reference discloses variants of *Anemonia sulcata* chromoprotein that have emission peaks that are red shifted up to 610 nm.

In the spirit of expediting prosecution and without conceding as to the correctness of the rejection, the claims have been amended to remove the term "about" and to recite "ranging from 620 to 680 nm".

As such, since the cited reference fails to teach fluorescence protein "having a emission maximum ranging from 620 to 680 nm", the cited reference fails to teach each and every element as found in the claims. Therefore, the Applicants respectfully request that this rejection be withdrawn.

Min et al. (Office Action, page 21)

The Office Action has rejected Claims 3-4, 7-12 and 18-24 under 35 U.S.C. § 102(b) for allegedly being anticipated by Min et al., Biochem. Biophys. Comm. 265:273-278 (1999). In view of the amendments to the claims, this rejection may be withdrawn.

The cited reference discloses the fluorescent qualities of the *Photinus pyralis* luciferase. The beetle *Photinus pyralis* is from the phylum *Arthropodea*.

In the spirit of expediting prosecution and without conceding as to the correctness of the rejection, the claims have been amended to recite "a fluorescent ***Stichodactylidaen*** protein".

As such, since the cited reference fails to teach a fluorescent protein from the phylum *Cnidaria*, the cited reference fails to each and every element as found in the claims. Therefore, the Applicants respectfully request that this rejection be withdrawn.

Tsien et al. (Office Action, page 23)

The Office Action has rejected Claims 5-12 and 18-24 under 35 U.S.C. § 102(a) for allegedly being anticipated by Tsien et al., U.S. Patent No. 6,342,379. In view of the amendments to the claims, this rejection may be withdrawn.

The Office Action notes asserts that the cited reference discloses a sequence that is 100% identical to a nucleotide sequence of at least 10 residues in length of SEQ ID NO:11 (Office Action, page 24). Moreover, the Office Action objects to the language "a nucleotide sequence of SEQ ID NO:11".

In the spirit of expediting prosecution and without conceding as to the correctness of the rejection, the claims have been amended to remove the objectionable language and to recite "a sequence identity of at least about 75% (80%, or 90%) with SEQ ID NO:11".

As such, since the cited reference fails to teach each and every element as found in the claims, the cited reference fails to anticipate the claims. Therefore, the Applicants respectfully request that this rejection be withdrawn.

Rejection Under Obvious-Type Double Patenting

Application No. 10/006,922

The Office Action has maintained the provisional rejection of Claims 1-2, 7-12 and 18-24 under the judicially created doctrine of obviousness-type double patenting over Claims 1-5, 8-10, 12-15, and 22-23 of co-pending Application No. 10/006,922. This rejection is respectfully traversed.

In maintaining the rejection, the Office Action objects to the use of the phrase "a nucleotide sequence". In particular, the Office Action states that the phrase encompasses "any segment/portion of the nucleotide sequence of SEQ ID NO:11" (Office Action, page 4). As noted above, for further clarity the claims have been amended remove the objectionable language and to recite "**wherein said nucleic acid**

has a sequence identity of at least about 75% with SEQ ID NO: 11". In contrast, the co-pending '922 application does not disclose the nucleic acid sequence of SEQ ID NO:11.

Therefore, the Applicants respectfully request that this rejection be withdrawn.

Application No. 10/081,864

The Office Action has maintained the provisional rejection of claims 1-2, 7-12 and 18-24 under the judicially created doctrine of obviousness-type double patenting over Claims 1-3, 5-9, and 15-16 of co-pending Application No. 10/081,864. This rejection is respectfully traversed.

In maintaining the rejection, the Office Action objects to the use of the phrase "a nucleotide sequence". In particular, the Office Action states that the phrase encompasses "any segment/portion of the nucleotide sequence of SEQ ID NO:11" (Office Action, page 4). As noted above, for further clarity the claims have been amended remove the objectionable language and to recite "**wherein said nucleic acid has a sequence identity of at least about 75% with SEQ ID NO: 11**". In contrast, the co-pending '864 application does not disclose the nucleic acid sequence of SEQ ID NO:11.

Therefore, the Applicants respectfully request that this rejection be withdrawn.

Application No. 10/155,809

The Office Action maintains the provisional rejection of claims 1-12 and 18-24 under the judicially created doctrine of obviousness-type double patenting over claims 1-16, 21 and 43 of co-pending Application No. 10/155,809. This rejection is respectfully traversed.

In maintaining the rejection, the Office Action objects to the use of the phrase "a nucleotide sequence". In particular, the Office Action states that the phrase

encompasses "any segment/portion of the nucleotide sequence of SEQ ID NO:11" (Office Action, page 4). As noted above, for further clarity the claims have been amended remove the objectionable language and to recite "**wherein said nucleic acid has a sequence identity of at least about 75% with SEQ ID NO: 11**". In contrast, the co-pending '809 application does not disclose the nucleic acid sequence of SEQ ID NO:11.

Therefore, the Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

In view of the above remarks, this application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issuance.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: March 29, 2006

By: _____
Edward J. Baba
Registration No. 52,581

Date: 3.29.06

By: _____
Bret E. Field
Registration No. 37,620

Enclosures:

- Replacement Figures 1, 2, 4, 6, 8, 10, 12, 13, 15, 16, and 17.
- Sequence Listing

BOZICEVIC, FIELD & FRANCIS LLP
1900 University Avenue, Suite 200
East Palo Alto, CA 94303
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

F:\DOCUMENT\CLON\028\response to office action of 1-3-06 (CLON-028).DOC